

RECOMBINANT DNA ADVISORY COMMITTEE
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A PHASE I/II, OPEN-LABEL DOSE ESCALATION STUDY
TO EVALUATE THE SAFETY AND EFFICACY OF
SINGLE DOSES OF TT-034 IN PATIENTS WITH
CHRONIC HEPATITIS C (CHC) INFECTION

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Key Personnel

Duke University – Clinical Site

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Background

HCV: 130 - 150 million infected worldwide. Leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation

Current SoC for Genotype 1: triple therapy up to 48 weeks.

- Cure rates up to 75%
- Associated with severe side effects
- Compliance issues

New therapies on horizon are all-oral, interferon free treatment for 8 or 12 weeks.

- Cure rates between 40 - 90% in early clinical trials

However, the need for better treatments remain

- An ideal treatment would be very short duration, have high cure rates, almost no side effects and broad coverage

TT-034: Many Attributes of an “Ideal” Therapy for HCV

TT-034 is an RNAi therapeutic that is intended as a “one-shot-cure”

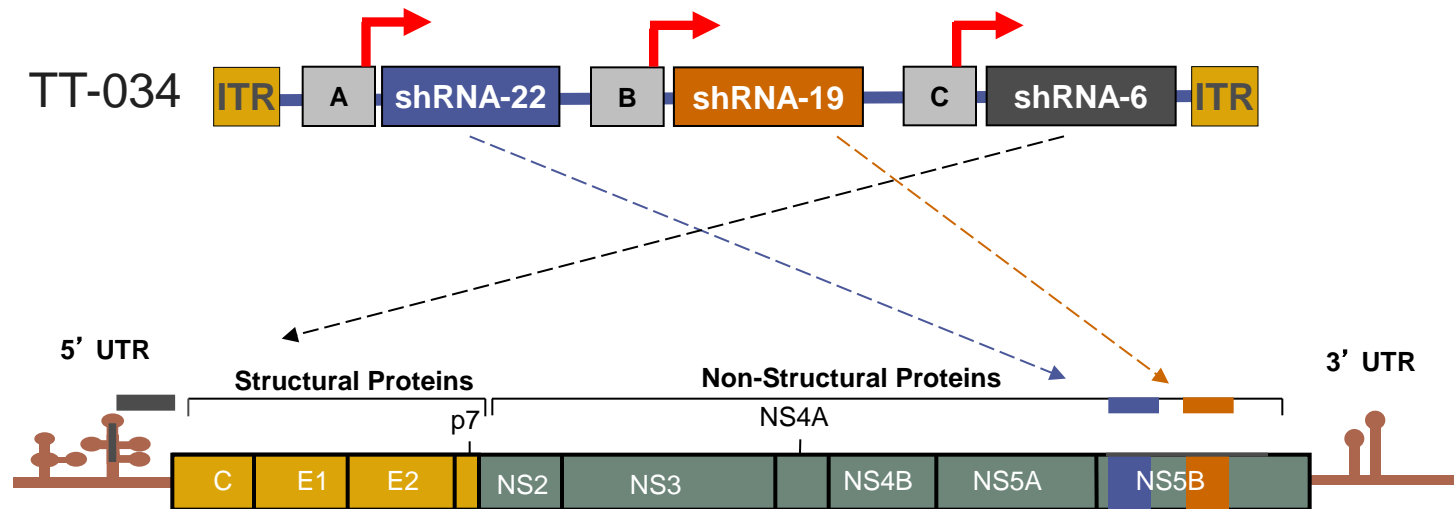
- Recombinant AAV genome delivered via an AAV8 vector (high liver tropism)
- Continuously produces replenishing pool of shRNAs for over 180 days
- shRNA target three separate, well conserved regions of HCV RNA genome
- Capability for near complete hepatocyte transduction

Goal is to achieve complete elimination of virus or SVR with a single infusion

- Eliminates long treatments and patient compliance issues
- Very low toxicity in animal studies
- Potential for combination with small molecules therapies
- Non-responders to TT-034 can go on to standard therapies

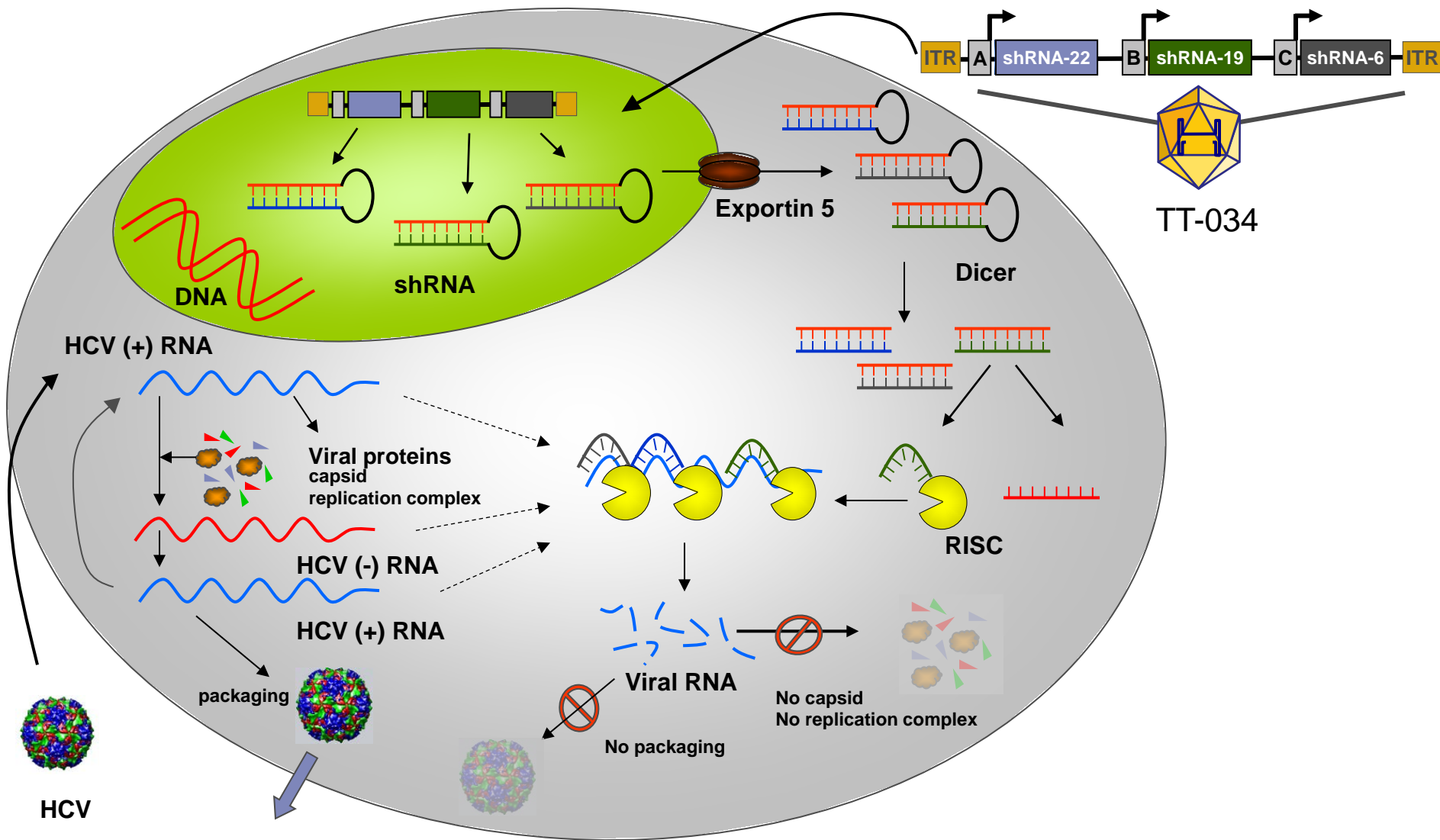
However, once administered no ability to withdraw therapy

Overview of Expression Cassette from TT-034

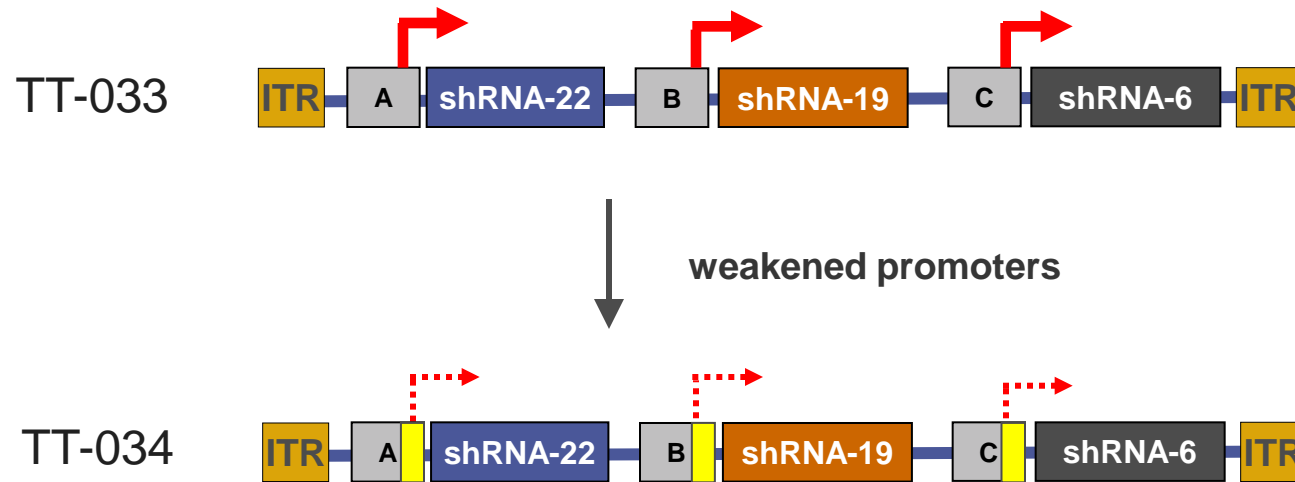


- 3 independently transcribed RNAi elements target 3 separate, well-conserved regions of the HCV genome; helps prevent the generation of viral escape mutants
- Combination drug in one therapeutic entity provides broad patient applicability, while maintaining specificity

MOA of TT-034 Against the HCV Infectious Cycle



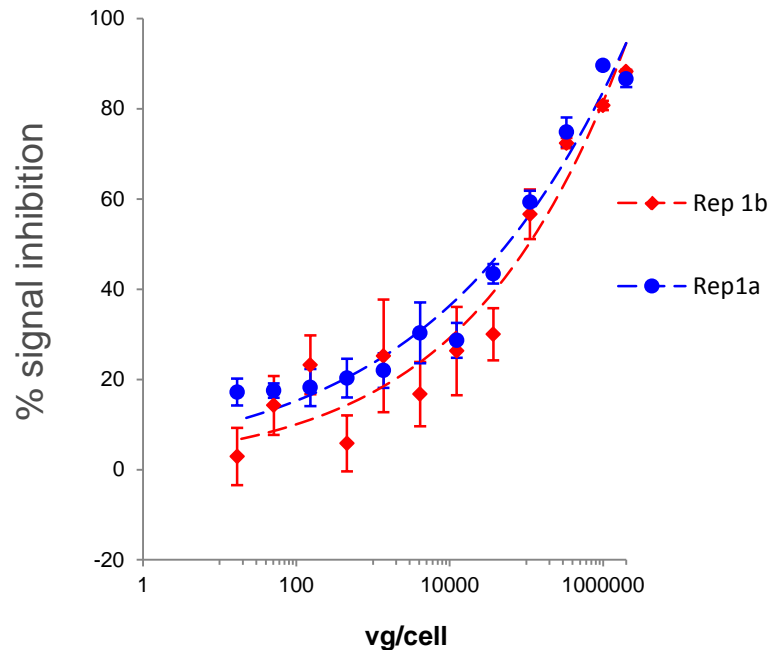
TT-034: Optimized for Safety and Efficacy



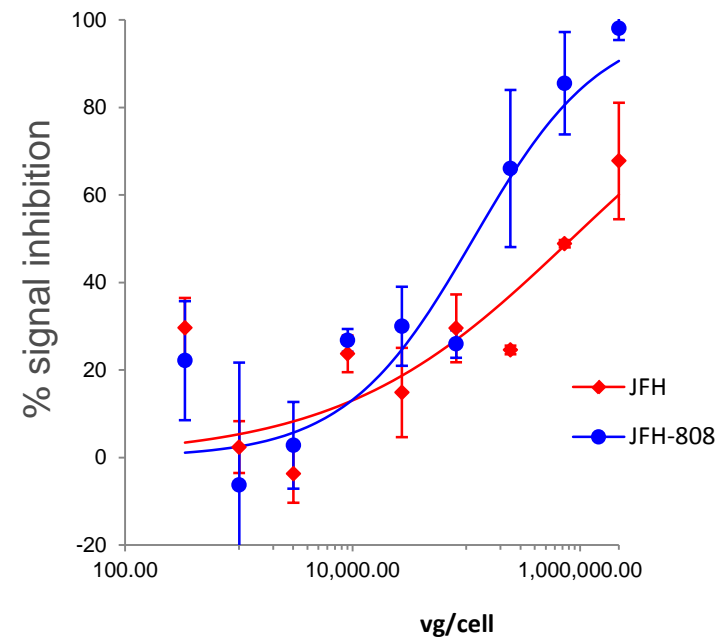
- First generation TT-033 toxicity associated with very high shRNA levels
- Modifications to the U6 promoters to reduce expression of shRNA
- AAV8 delivery vehicle remains the same resulting in identical transduction and biodistribution properties

TT-034 Activity Against Genotype 1a and 1b HCV Replicon Models and an Infectious Tissue Culture System

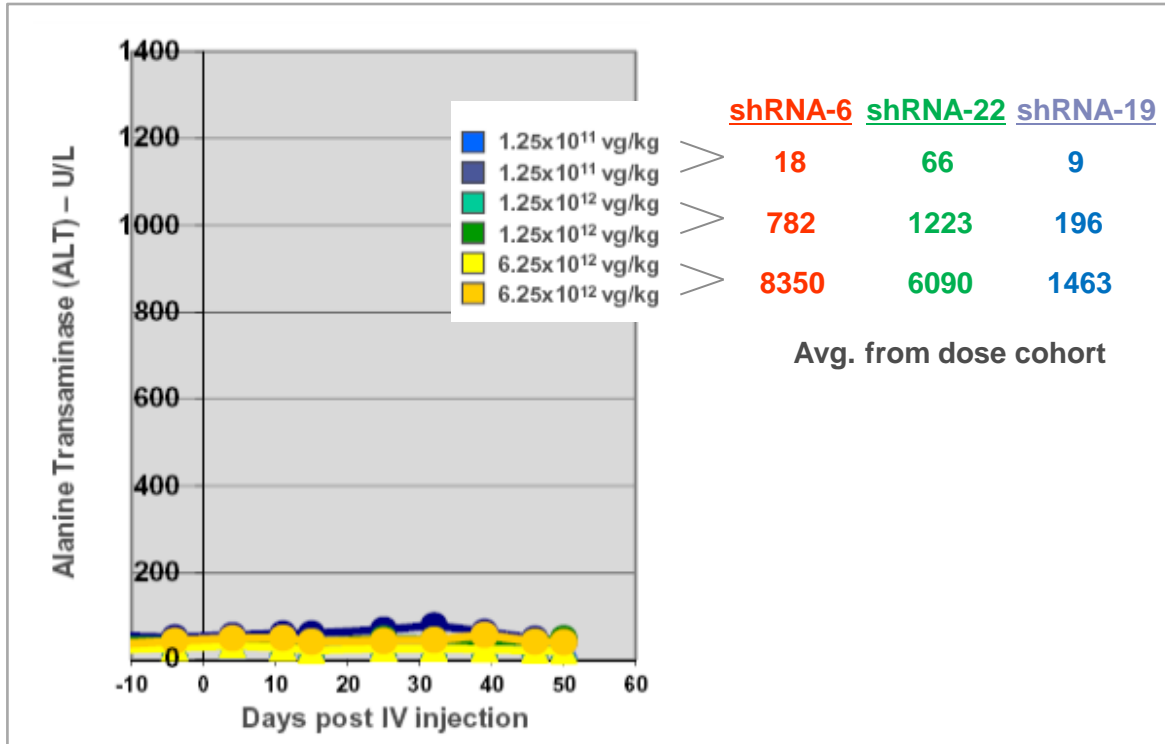
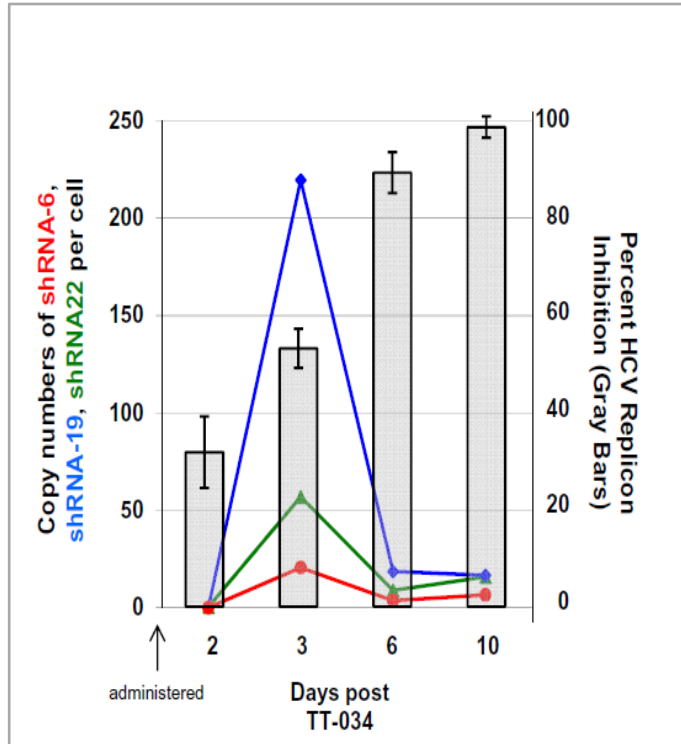
HCV replicon
(representative data)



HCVcc
(representative data)



TT-034: Clinically Relevant Doses Produce Predictive Efficacious shRNA Levels in the Absence of Liver Toxicity



shRNA expression eliminates virus

Minimal liver toxicity in NHPs

shRNA/cell in NHPs

Summary of TT-034 GLP Safety Data

Sustained and preferential transduction of hepatocytes with concomitant shRNA expression.

- 180 Day GLP studies in 520 mice and 80 NHPs at 3 dose levels

Minimal and transient adverse events

- No test article-related findings in clinical observations, body weights, food consumption, hematology, cytokines, gross pathology, or organ weights.
- In NHPs: highest dose only (1×10^{13} vg/kg) associated with transient increased ALT and AST on Day 4. Unlikely due to transgene expression. Resolved by 3 weeks.
- In mice minimal vacuolation in the zona fasciculata of the adrenal glands in 1/15 males at middle dose (1×10^{12} vg/kg) and 4/15 males at high dose (1×10^{13} vg/kg) only at day 15 necropsy. Considered non-adverse.
- No significant miRNA safety findings

Outline of Clinical Protocol

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Phase I/II Study Design

- Open label, single-dose, dose escalation safety study in 14 HCV genotype 1 patients
- 5 dose cohorts
- DSMB review after first patient in each cohort and between cohorts
- Extensive safety monitoring during 24 weeks observation
- Liver biopsy at day 21 (expected peak shRNA expression); assays for DNA transduction, shRNA expression, histopathology

Endpoints Through Week 24

Primary Endpoints (Safety):

- Incidence of treatment-emergent adverse events
- Changes in clinical and laboratory parameters

Secondary Endpoints (Efficacy, PK, and PD):

- Change in HCV viral load
- Assessment of viral vector DNA levels in liver biopsy
- Assessment of shRNA expression in liver biopsy
- shRNA expression levels in exosomes in serum
- Blood vector DNA levels in serum

Inclusion Criteria

1. Signed Informed Consent Form
2. ≥ 18 years old and ≤ 65 years of age
3. Females of non-childbearing potential
4. Males and their partners must be willing to comply with double barrier contraception
5. A history of chronic HCV genotype 1 infection with baseline HCV RNA level of $> 100,000$ IU/mL, and one or more of the following:
 - Treatment failures or relapse to current SoC
 - Ineligible or unwilling to receive current SoC
6. No evidence of cirrhosis at screening
7. Alanine aminotransferase levels $\leq 4 \times$ the ULN
8. At least 3 months since prior therapy for HCV

Exclusion Criteria

1. Body mass index < 18.5 or > 30 .
2. Serum Neutralizing Antibodies to AAV8 (may abrogate transduction)
3. Signs of severe liver disease
4. Hepatocellular carcinoma or suspicion of HCC
5. Positive for human immunodeficiency virus 1 (HIV1) or HIV2 antibody
6. Co-infection with hepatitis B virus
7. Treatment with an investigational drug within 6 months
8. Received an AAV vector at any time, or any other gene transfer agent in the previous 6 months
9. Use of immunosuppressive medications within 6 months before, except for inhaled or topical corticosteroids.

Dose Escalation Scheme

	4.00×10^{10}	Starting dose	2	Sequential (1+1)	6 week
	1.25×10^{11}	0.5	3	Sequential and parallel (1+2)	6 week
	4.00×10^{11}	0.5	3	Sequential and parallel (1+2)	6 week
	1.25×10^{12}	0.5	3	Sequential and parallel (1+2)	10 weeks
	4.00×10^{12}	0.5	3	Sequential and parallel (1+2)	10 weeks

Starting dose 250-fold less than the NOAEL in nonclinical studies

Pre-Trial Screening Assessments

- Informed Consent
- Medical History
- Full Physical Examination
- Height, weight, vital signs
- Existing AEs
- Concomitant medication(s)
- Alcohol consumption history
- Liver enzymes and liver function
- Urine drug screen
- ECG
- Clinical laboratory tests
- Serum pregnancy test
- HCV enzyme immunoassay
- HCV genotype
- HIV, HBV serology
- Troponin I & T
- **nAb to AAV8**
- **IFN γ -ELISpot to AAV8**
- HCV viral load
- Liver MR elastography or Fibroscan or biochemical fibrosis test
- Review of historical liver biopsy
- Chest X-ray
- Ultrasound of the liver
- Alpha-fetoprotein
- Anti-smooth muscle antibody
- Viral vector in body fluids
- HCV target site sequencing

Assessments During the 24 Weeks Observation Period

- PE
- Weight and vital signs
- Cytokines
- ESR, CRP, and complement C3/C4
- ECG
- **Liver enzymes and liver function**
- Clinical lab tests
- **Troponin I&T**
- **Morning fasting serum cortisol**
- **nAb to AAV8**
- **IFN γ -ELISpot to AAV8**
- **Viral vector in body fluids**
- **HCV viral load**
- **HCV target site sequencing**
- **Liver biopsy** (day 21) to assess DNA transduction, shRNA expression and histopathology
- Blood shRNA level (exosomes)
- Serum pregnancy test
- Ultrasound of the liver
- Alpha-fetoprotein

Dose Escalation Criteria and Stopping Rules

Dose escalation criteria

Dose cohort can be extended:

- In the event of the occurrence of one episode of DLT.
- If 2 subjects in the same cohort experience different DLTs

Dosing at a specific level will be stopped:

- In the event of occurrence of 2 episodes of the same DLT.

Stopping rules

Dosing will be stopped for the following:

- Death
- Grade 3 or Grade 4 toxicity if possibly related to study drug.
- ALT elevation to $> 10 \times$ baseline or elevation to > 500 U/L.
- Bilirubin elevation to $> 2 \times$ baseline if possibly related
- Increased INR to > 1.5 if possibly related
- Any other serious adverse event that is possibly related to study drug.

Program Summary

- TT-034 is a novel treatment modality for HCV
 - RNAi based treatment with gene vector that produces shRNA long term
 - Targets three regions of HCV genome reduces likelihood of escape mutants
- Nonclinical data support progressing TT-034 to clinical development
- Phase I/II study with careful dose escalation and extensive monitoring
- Goal is a “one-shot-cure”
- Potential for paradigm shift in HCV treatment